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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

AKHAVAN, RAMIN

ART UNIT	PAPER NUMBER
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1636

16

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Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary	Application No. 09/927,811	Applicant(s) ROMANO ET AL.	
	Examiner Ramin (Ray) Akhavan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-59 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 30-59 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

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DETAILED ACTION

Priority

Applicant's claim for priority based on prior application PCT/EP00/01144 filed on February 11, 2000 is acknowledged and accepted. In addition acknowledgment is made of applicant's claim for foreign priority based on an application filed in Switzerland on February 11, 1999. It is noted however that applicant has not filed a certified copy of the Swiss provisional application as required by 35 U.S.C. 119(b). Applicant must submit a certified translated copy.

Claim Objections

1. Claims 44 and 53 are objected to because of the following informalities: Claims' subparts are numbered using lower case roman numerals while other claims use lower case letters. For the sake of consistency lower case letters should also be used in claims 44 and 53. Appropriate correction is required.
2. Claim 53 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 53(i) when referring to the heat-inducible promoter the claim contains the word "a" versus "the". Because the claim is ultimately dependent from claim 30, which articulates possible promoters, the claim is limited to promoters therein; "a" indicates broader scope versus "the", thus making the claim as broader. Presumably applicant is not claiming any heat inducible promoter but only those articulated in claim 30.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is vague because applicant claims a method of expressing protein but there are no steps following the preamble. The claim is actually drawn to a vector (a) and a host cell capable of expressing protein (b). Thus the claim is actually a composition claim not a method claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 30-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for each claim's rejection will be addressed below.

Applicant's invention relates to nucleic acid molecules comprising a heat-inducible promoter element of the trehalose-6-phosphate gene in *H. polymorpha*, as well as expression vectors and host cells containing at least one inventive nucleic acid

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molecule. The invention further relates to kits and methods for producing one or more proteins using the inventive nucleic acid molecule. The aim of the invention is to provide a selective heat-inducible promoter that is suitable for the protein expression at high temperatures. Applicant defines "heat inducible promoter" as a promoter that brings about an increase in transcription of a gene of at least 50 percent where the gene is under control of the promoter that is responsive to a temperature increase of from 25°C to at least 37°C.

The instant specification discloses the entire sequence for the promoter element (SEQ ID NO: 1), as well as the entire nucleotide sequence for the trehalose-6-phosphate gene (SEQ ID NO: 6). There is a single example provided disclosing a correlation between nucleotides 228-792 from SEQ ID NO: 1 and function as a heat-inducible promoter. However the claims as written are drawn to entire genus of nucleic acids that allegedly would have heat-inducible promoter function.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. The disclosure only provides a single species (i.e. nucleotides 228-792 of SEQ ID 1).

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Claim 30(c) is drawn to a nucleic acid molecule comprising a heat-inducible promoter selected from a group members of which include: nucleic acid sequences that exhibit at least 40 percent identity over any 300bp stretch with either SEQ ID NO: 1 or the promoter sequence of *H. Polymorpha* gene encoding a protein with trehalose-6-phosphate synthase activity. Thus claim 30 is drawn to a broad genus of potential nucleic acids but the specification does not teach a correlation between the structures encompassed by the claim and their function as a heat-inducible promoter as defined in the specification. The same analysis applies to 30(e), which as written can be drawn to any size deletion, substitution or addition but again there is nothing in the disclosure or in the art that would indicate there would be a correlation between structure and function as between the genus claimed and the species disclosed in the specification.

Claims 31-34 are drawn to nucleic acid sequences exhibiting 60, 80, 90 and 95 percent identity respectively, over any 300 bp stretch of sequence from either 30(a) or (b). Again the claims are drawn to a genus of potential nucleic acid molecules while the specification only provides a single representative species (i.e. nucleotides 228-792). Claims 35-59 depend from claim 30 thus are also rejected.

In addition claims 41 and 42 are drawn fragments from SEQ ID 1 (i.e. respectively they are nucleotides 492-792 and 627-713) but there is nothing in the specification or in the art to suggest that these fragments would function as heat-inducible promoter elements. The specification only clarifies the promoter element down to nucleotides 228-792, i.e. claim 40 which contains allowable subject matter but for it's dependence from claim 30.

It must therefore be considered that the single disclosed species is not a representative number of species sufficient to convince the skilled artisan that applicant is in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

102(a)

5. Claim 30-42, 44, 47-49, 51-54 and 56-59 are rejected under 35 U.S.C. 102(a) as being anticipated by Reinders, A. et al. The Thermophilic Yeast *Hansenula polymorpha* Does Not Require Trehalose Synthesis for Growth at High Temperatures but Does for Normal Acquisition of Thermotolerance. *J. Bacteriology*, 181(15): 4665-4668 (Aug. 3, 1999). Applicant claims the nucleic acid sequence, which encodes the polypeptide having trehalose-6-phosphate synthase activity and the heat inducible promoter element for said gene as well as expression vectors comprising said gene/promoter element. Furthermore applicant claims “non-naturally” occurring host cell containing the isolated nucleic acid containing heat-inducible promoter activity and heat shock elements.

Reinders isolates the *H. polymorpha* trehalose-6-phosphate gene including the promoter, which contains the heat shock elements or heat-inducible elements (claims 30-40). Id. at 4665. Furthermore Reinders teaches use of a fragment of the promoter region,

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0.6 and 1.0 kb upstream of the start site to assess heat-inducibility of said promoter regions (claims 40-42). Id. At 4667. In addition Reinders teaches an expression vector used to express *H. polymorpha* trehalose-6-phosphate in non-naturally occurring host *S. cerevisiae*(claims 47-49, 51-54 and 56-59). Id. at 4666, column 2.

Both applicant and Reinders teach the same sequence (i.e. SEQ ID NO: 6 which contains SEQ ID NO: 1), thus the biological activities associated with said sequence would be inherent. Furthermore both applicant and Reinders teach incorporating said sequence in an expression vector and expressing protein in a non-naturally occurring host, such as *S. cerevisiae*. Thus Reinders anticipates above referenced claims.

It is noted however if foreign priority is granted based on a provisional application filed in Switzerland on February 11, 1999 that the basis for this rejection would be obviated. *See supra* ¶ Priority.

102(b)

6. Claims 30, 47-49 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Xiao-Dong et al. Conservation of a stress response: human heat shock transcription factors functionally substitute for yeast HSF (November 1, 1997) EMBO, 16(21): 6466-6477.

Claim 30(e) is drawn to a heat-inducible promoter consisting of a “derivative” of either a nucleic acid comprising the promoter of trehalose-6-phosphate from *H. polymorpha*, or sequence of SEQ ID NO: 1, or a nucleic acid having a sequence with at least 40 percent identity over any 300 bp stretch of either of the preceding sequences. The term ‘derivative’ could mean any substitution, deletion or addition when interpreted

broadly. Thus a heat-inducible promoter that shares the smallest degree of similarity (i.e. a single nucleotide) would read on claim 30.

Claims 47-49 relate to a heat-inducible promoter of claim 30 that occurs in a non-naturally occurring host (claim 47) wherein the host is fungal (claim 48) and furthermore the fungal cell is yeast (claim 49).

Claim 51 relates to placing a promoter found in claim 30 into an expression vector; claim 42 comprises a kit using an expression vector of claim 51 and host cells suitable for heat-inducible production of protein; and claim 53 relates to a method of producing recombinant protein using the expression vector in claim 51.

Xiao-Dong teaches a human heat shock gene promoter element that is heat-inducible and that has nucleic acids reading on claim 30(e). Xiao-Dong at 6471, column 2. In addition the promoter element is heat-inducible at 37°C and 50°C thus it meets applicant's definition of heat-inducible promoter. Id. at 6475 and Fig. 8. Furthermore the promoter increases expression of heterologously linked gene by 10-fold. Id. at 6472 column 2.

In addition Xia-Dong teaches use of this promoter in a non-naturally occurring host cell that is *S. cerevisiae*; this reads on claims 47-49. Id. at 6468-6469 and Fig. 2. Furthermore the heat-inducible promoter is used to express recombinant protein (i.e. heat-shock protein-fused with green fluorescent protein) through use of an expression vector introduced into a suitable host cell followed by heat-induced expression of the protein, thus meeting the limitations of claims 51-53. In light of the considerations articulated above Xia-Dong anticipates claims 30, 47-49 and 51-53.

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Conclusion


Applicant needs to submit certified translated copy of Swiss provisional application. Claims 30-59 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

August 11, 2003


DAVID GUZO
PRIMARY EXAMINER